(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number
WO 02/059088 A1

(51) International Patent Classification[7]: C07D 209/08, 405/12, 231/56, 409/12, A61P 25/28, A61K 31/4045, 31/416, 31/4184.

(21) International Application Number: PCT/US02/01950

(22) International Filing Date: 18 January 2002 (18.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/263,425 23 January 2001 (23.01.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/059088 A1

(54) Title: 1-ARYL-OR 1-ALKYLSULFONYLBENZAZOLE DERIVATIVES AS 5-HYDROXYTRYPTAMINE-6 LIGANDS

(57) Abstract: The present invention provides a compound of formula I and the use thereof for the therapeutic treatment of disorders relating to or affected by the 5-HT6 receptor.

1-ARYL-OR 1-ALKYLSULFONYLBENZAZOLE DERIVATIVES AS 5-HYDROXYTRYPTAMINE-6 LIGANDS

This invention relates to 1-aryl- or 1-alkylsulfonylbenzazole derivatives useful as 5-hydroxytryptamine-6 ligands, to processes for preparing them, to pharmaceutical compositions containing them and to methods of treatment using them.

BACKGROUND OF THE INVENTION

Various central nervous system disorders such as anxiety, depression, motor disorders, etc., are believed to involve a disturbance of the neurotransmitter 5-hydroxytryptamine (5-HT) or serotonin. Serotonin is localized in the central and peripheral nervous systems and is known to affect many types of conditions including psychiatric disorders, motor activity, feeding behavior, sexual activity, and neuroendocrine regulation among others. The effects of serotonin are regulated by the various 5-HT receptor subtypes. Known 5-HT receptors include the 5-HT1 family (e.g. 5-HT1A), the 5-HT2 family (e.g. 5-HT2A), 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5-HT7 subtypes.

The recently identified human 5-hydroxytryptamine-6 (5-HT6) receptor subtype has been cloned, and the extensive distribution of its mRNA has been reported. Highest levels of 5-HT6 receptor mRNA have been observed in the olfactory tubercle, the striatum, nucleus accumbens, dentate gyrus and CA1, CA2 and CA3 regions of the hippocampus. Lower levels of 5-HT6 receptor mRNA were seen in the granular layer of the cerebellum, several diencephalic nuclei, amygdala and in the cortex. Northern blots have revealed that 5-HT6 receptor mRNA appears to be exclusively present in the brain, with little evidence for its presence in peripheral tissues. The high affinity of a number of antipsychotic agents for the 5-HT6 receptor, in addition to its mRNA localization in striatum, olfactory tubercle and nucleus accumbens suggests that some of the clinical actions of these compounds may be mediated through this receptor. Therefore, 5-HT6 receptor ligands are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorder, attention defecit disorders, migraine, cognitive memory enhancement (e.g. for the treatment of Alzheimer's disease), sleep disorders, feeding disorders (e.g. anorexia or bulimia), neurodegenerative disorders (e.g. head trauma or stroke),panic attacks, withdrawal from drug abuse (e.g. cocaine, ethanol, nicotine or benzodiazepines), schizophrenia, or the like; or in the treatment of certain gastrointestinal disorders such as irritable bowel syndrome.

Therefore, it is an object of this invention to provide compounds which are useful as therapeutic agents in the treatment of a variety of central nervous system disorders related to or affected by the 5-HT6 receptor.

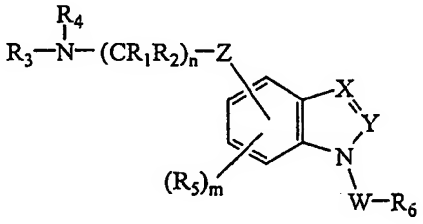
It is another object of this invention to provide therapeutic methods and pharmaceutical compositions useful for the treatment of central nervous system disorders related to or affected by the 5-HT6 receptor.

It is a feature of this invention that the compounds provided may also be used to further study and elucidate the 5-HT6 receptor.

These and other objects and features of the invention will become more apparent by the detailed description set forth hereinbelow.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



(I)

wherein

W is SO_2, CO, CONH, CSNH or CH_2;

X is CR_7 or N;

Y is CR_8 or N with the proviso that when X is N, then Y must be CR_8;

Z is O, SO_p or NR_9;

R_1 and R_2 are each independently H or C_1-C_6alkyl;

n is an integer of 2, 3 or 4;

R_3 and R_4 are each independently H, $CNR_{10}NR_{11}R_{12}$ or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted, or R_3 and R_4 may be taken together with the atom to which they are attached to form an optionally substituted 3- to 6-membered ring optionally containing an additional heteroatom selected from O, N or S;

R_5 is H, halogen, CN, OR_{13}, CO_2R_{14}, $CONR_{15}R_{16}$, $CNR_{17}NR_{18}R_{19}$, $SO_2NR_{20}R_{21}$, SO_qR_{22} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

m is an integer of 1, 2 or 3;

p and q are each independently 0 or an integer of 1 or 2;

R_6 is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

R_7 and R_8 are each independently H, halogen or a C_1-C_6 alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_9 is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{10}, R_{11}, R_{12}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19} are each independently H or C_1-C_4alkyl;

R_{13} is H, COR_{23} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{14} is H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted;

R_{20} and R_{21} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{22} and R_{23} are each independently an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group; or a pharmaceutically acceptable salt thereof.

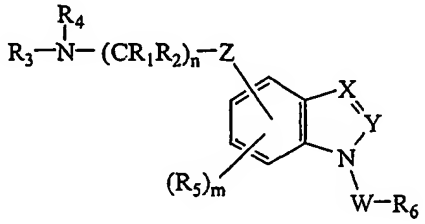
The present invention also provides methods and compositions useful for the therapeutic treatment of central nervous system disorders related to or affected by the 5-HT6 receptor.

DETAILED DESCRIPTION OF THE INVENTION

The 5-hydroxytryptamine-6 (5-HT6) receptor is one of the most recent receptors to be identified by molecular cloning. Its ability to bind a wide range of therapeutic compounds used in psychiatry, coupled with its intriguing distribution in the brain has stimulated significant interest in new compounds which are capable of interacting with or affecting said receptor. At present, there are no known fully selective agonists. Significant efforts are being made to understand the possible role of the 5-HT6 receptor in psychiatry, cognitive dysfunction, motor function and control, memory, mood and the like. To that end, compounds which demonstrate a binding affinity for the 5-HT6 receptor are earnestly sought both as an aid in the study of the 5-HT6 receptor and as

potential therapeutic agents in the treatment of central nervous system disorders.

Surprisingly, it has now been found that 1-aryl- or 1-alkylsulfonylbenzazole derivatives of formula I demonstrate 5-HT6 affinity. Advantageously, said benzazole derivatives may be used as effective therapeutic agents for the treatment of central nervous system (CNS) disorders associated with or affected by the 5-HT6 receptor. Accordingly, the present invention provides 1-alkyl- or 1-arylsulfonylbenzazole derivatives of formula I



(I)

wherein

W is SO_2, CO, CONH, CSNH or CH_2;

X is CR_7 or N;

Y is CR_8 or N with the proviso that when X is N, then Y must be CR_8;

Z is O, SO_p or NR_9;

R_1 and R_2 are each independently H or C_1-C_6alkyl;

n is an integer of 2, 3 or 4;

R_3 and R_4 are each independently H, $CNR_{10}NR_{11}R_{12}$, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted, or R_3 and R_4 may be taken together with the atom to which they are

attached to form an optionally substituted 3- to 6-membered ring optionally containing an additional heteroatom selected from O, N or S;

R_5 is H, halogen, CN, OR_{13}, CO_2R_{14}, $CONR_{15}R_{16}$, $CNR_{17}NR_{18}R_{19}$, $SO_2NR_{20}R_{21}$, SO_qR_{22} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

m is an integer of 1, 2 or 3;

p and q are each independently 0 or an integer of 1 or 2;

R_6 is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

R_7 and R_8 are each independently H, halogen or a C_1-C_6 alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_9 is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{10}, R_{11}, R_{12}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19} are each independently H or C_1-C_4alkyl;

R_{13} is H, COR_{23} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

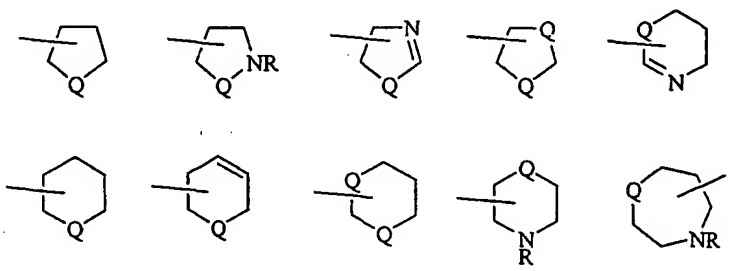
R_{14} is H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted;

R_{20} and R_{21} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{22} and R_{23} are each independently an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group; or

a pharmaceutically acceptable salt thereof.

As used in the specification and claims, the term halogen designates Br, Cl, I or F and the term aryl denotes an aromatic hydrocarbon of 6 to 10 carbon atoms such as phenyl and naphthyl. The term cycloheteroalkyl designates a 5 to 7 membered ring system containing 1 or 2 heteroatoms, which may be the same or different, selected from N, O or S and optionally containing one double bond. Exemplary of the cycloheteroalkyl ring systems included in the term as designated herein are the following rings wherein Q is NR, O or S; and R is H or an optional substituent as defined hereinbelow.



For example the term cycloheteroalkyl includes radicals derived from rings such as piperidine, morpholine, piperazine and pyrrolidine.

Similarly, as used in the specification and claims, the term heteroaryl designates a 5 to 10 membered aromatic ring system containing 1 or 2 heteroatoms, which may be the same or different, selected from N, O or S, e.g., mono- or bi-cyclic. Such heteroaryl ring systems include pyrrolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furyl, thienyl, quinolinyl, isoquinolinyl, indolinyl, benzothienyl, benzofuranyl, benzisoxazolyl and

the like; the term haloalkyl designates a C_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different; and the term haloalkoxy designates an OC_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different.

In the specification and claims, when the terms C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, cycloheteroalkyl, aryl or heteroaryl are designated as being optionally substituted, the substituent groups which are optionally present may be one or more of those customarily employed in the development of pharmaceutical compounds or the modification of such compounds to influence their structure/activity, persistence, absorption, stability or other beneficial property. Specific examples of such substituents include halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio, alkylsuphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy, cycloheteroalkyl, heteroaryl or cycloalkyl groups, preferably halogen atoms or lower alkyl groups of 1-6 carbon atoms. Typically, 0-3 substituents may be present. When any of the foregoing substituents represents or contains an alkyl substituent group, this may be linear or branched and may contain up to 12, preferably up to 6, more preferably up to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, and n- and t-butyl.

Pharmaceutically acceptable salts may be any acid addition salt formed by a compound of formula I and a

pharmaceutically acceptable acid such as phosphoric, sulfuric, hydrochloric, hydrobromic, citric, maleic, malonic, mandelic, succinic, fumaric, acetic, lactic, nitric, sulfonic, p-toluenesulfonic, methanesulfonic acid or the like.

Examples of R_6 are phenyl, naphthyl and heteroaryl groups as illustrated above each optionally substituted by substituents as defined hereinabove.

Examples of Y are N and CH.

Examples of X are CH and N.

R_1 and R_2 may each represent independently for example H or methyl.

An example of n is the integer 2.

Examples of R_3 and R_4 are independently H, methyl which may be substituted by substituents as herein defined, e.g. by optionally substituted phenyl such as C_1-C_6alkoxyphenyl; cycloheteroalkyl having a heteroatom selected from O or S and for example having six members eg pyranyl or thiopyranyl which which ring may be optionally substituted;
or R_3 and R_4 may together with the nitrogen represent a six membered ring such as morpholinyl or piperidinyl which ring may be optionally substituted.

Examples of optional substituents for aryl (e.g. phenyl) or aryl substituted alkyl groups (e.g. benzyl) are halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio, alkylsuphinyl,

alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl and benzyloxy and cycloheteroalkyl, heteroaryl cycloalkyl groups as illustrated hereinabove.

Preferred compounds of the invention are those compounds of formula I wherein W is SO_2 or CO. Also preferred are those compounds of formula I wherein Z is O. Another group of preferred compounds of the invention are those compounds of formula I wherein n is 2. Further preferred compounds of the invention are those compounds of formula I wherein R_6 is an aryl or heteroaryl group each optionally substituted.

More preferred compounds of the invention are those compounds of formula I wherein W is SO_2; R_1 and R_2 are H; and n is 2. Another group of more preferred compounds of the invention are those compounds of formula I wherein W is SO_2; Z is O; X is CR_7; and R_3 and R_4 are taken together with the atom to which they are attached to form a 5- or 6-membered ring optionally containing one oxygen atom.

Among the preferred compounds of the invention are:

2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethylamine;

4-(2-morpholin-4-ylethoxy)-1-(phenylsulfonyl)-1H-indole;

1-(phenylsulfonyl)-4-(2-piperidin-1-ylethoxy)-1H-indole;

N-(2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethyl)-tetrahydro-2H-pyran-4-amine;

N,N-bis(3-methoxybenzyl)-2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethanamine;

N-(3-methoxybenzyl)-2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethanamine;

N,N-dimethyl-2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethanamine;

1-(phenylsulfonyl)-4-[2-(1-piperidinyl)ethoxy]-1*H*-indazole;

2-{[1-(phenylsulfonyl)-1*H*-indazol-4-yl]oxy}ethylamine;

N-(2-{[1-(phenylsulfonyl)-1*H*-indazol-4-yl]oxy}ethyl)tetrahydro-2*H*-pyran-4-amine;

N-(2-{[1-(phenylsulfonyl)-1*H*-indazol-4-yl]oxy}ethyl)tetrahydro-2*H*-thiopyran-4-amine;

1-[(4-nitrophenyl)sulfonyl]-4-[2-(1-piperidinyl)ethoxy]-1*H*-indazole;

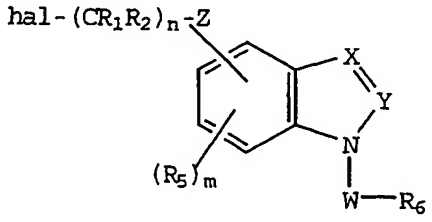
1-[(4-fluorophenyl)sulfonyl]-4-[2-(1-piperidinyl)ethoxy]-1*H*-indazole;

4-({4-[2-(1-piperidinyl)ethoxy]-1*H*-indazol-1-yl}sulfonyl)aniline; or

a pharmaceutically acceptable salt thereof.

This invention also provides processes for preparing compounds of formula (I) which comprise one of the following:

a) reacting a compound of formula (Va)



(Va)

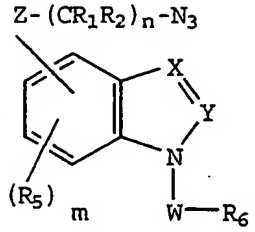
wherein hal is a halogen, e.g. chlorine or bromine and n, m, W, X, Y, Z, R_1, R_2, R_5 and R_6 are as defined herein, with an amine of formula

$$HNR_3R_4$$

wherein R_3 and R_4 are as defined herein, said reactants protected on reactive sites and/or on reactive substituent groups as required, and removing any protecting groups to give a corresponding compound of formula (I);

or

b) reducing a compound of formula (VIa)

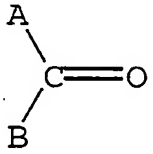


(V1a)

wherein n, m, Z, W, X, Y, R_1, R_2, R_3, R_5 and R_6 are as defined herein to give a compound of formula (I) wherein R_3 and R_4 are both H;

or

c) reductively alkylating a compound of formula (I) as defined herein wherein R_3 and R_4 are hydrogen with an alkylating agent of formula



where A and B independently represent H, or optionally substituted alkyl of 1-5 carbon atoms, alkenyl of 2-5 carbon atoms, alkynyl of 2-5 carbon atoms, aryl, heteroaryl or cycloheteroalkyl,
or A and B together represent an optionally substituted 3-6 membered cycloalkyl or cycloheteroalkyl ring,
to give a compound of formula (I)wherein R_3 and R_4 are both methyl, or R_3 is hydrogen and R_4 is optionally substituted alkyl of 1-6 carbon atoms, alkenyl of 2-6

carbon atoms, alkynyl of 2-6 carbon atoms, aryl-CH_2-, heteroaryl-CH_2-, cycloalkyl or cycloheteroalkyl;

or

d) converting a compound of formula (I) having a reactive substituent group to a different compound of formula I;

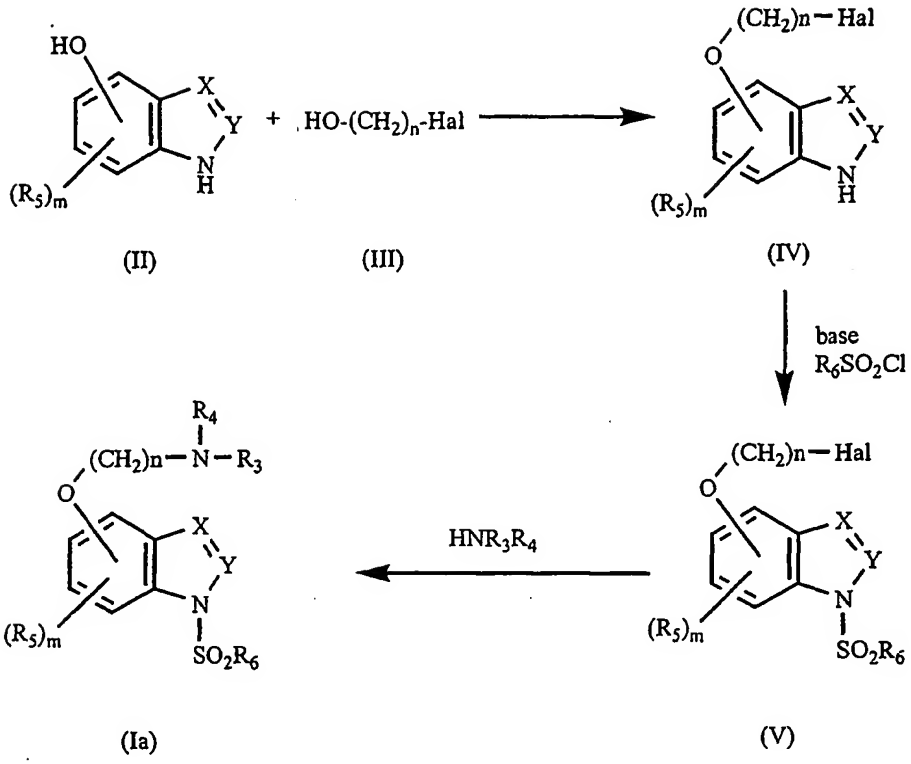
or

e) converting a basic compound of formula (I) to an acid addition salt or vice versa.

Where necessary in the processes described herein reactants may be protected on reactive sites and/or on reactive substituent groups using protecting groups.

Compounds of the invention may be prepared using conventional synthetic methods and, if required, standard separation and isolation techniques. For example, compounds of formula I wherein W is SO_2, R_1 and R_2 are H, and Z is O may be prepared by reacting an hydroxybenzazole intermediate of formula II with a haloalkanol of formula III in the presence of triphenylphosphine and diethyl azodicarboxylate to give the haloalkoxy derivative of formula IV; sulfonating the formula IV derivative to give the 1-sulfonylbenzazole compound of formula V; and displacing the halo group of said formula V compound with the appropriate amine to give the desired compounds of formula Ia. The reaction sequence is illustrated in flow diagram I wherein Hal designates a halogen atom.

FLOW DIAGRAM I

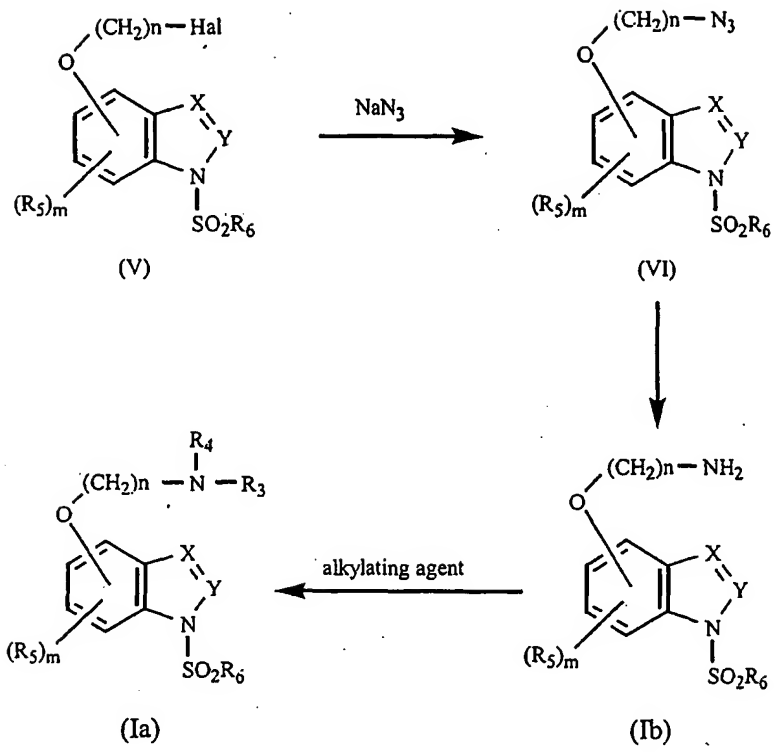


(II) (III) (IV)

(Ia) (V)

Alternatively, compounds of formula Ia may be prepared by reacting the intermediate of formula V with NaN_3 to form the corresponding benzazolyloxyalkylazide of formula VI; reducing said formula VI azide with triphenylphosphine to give the formula I compound wherein Z is O and R_1, R_2, R_3 and R_4 are H(Ib); and optionally alkylating said formula Ib compound to give compounds of formula Ia. The reactions are illustrated in flow diagram II.

FLOW DIAGRAM II

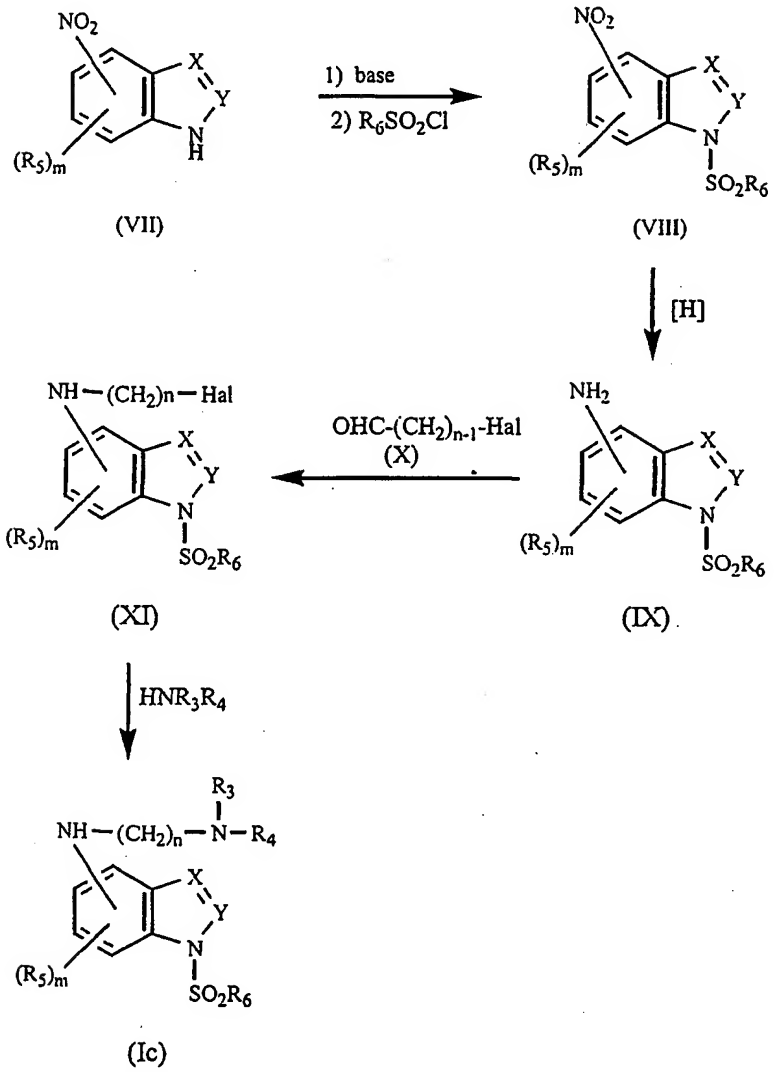


Similarly, compounds of formula I wherein W is SO_2 and Z is S may be prepared by utilizing the appropriate benzazolylthiol starting material and employing essentially the same reaction sequences shown hereinabove in flow diagrams I and II.

Compounds of formula I wherein W is SO_2 and Z is NH (Ic) may be prepared by sulfonating a nitrobenzazole intermediate of formula VII to give the corresponding 1-sulfonyl derivative of formula VIII; reducing the formula VIII compound to give the corresponding amine of formula IX; reacting said amine with a haloalkylaldehyde of formula X to give the haloalkylamine derivative of formula XI; and displacing the halo group of said formula XI derivative with the appropriate amine to give the

desired compounds of formula Ic. The reaction sequence is shown in flow diagram III.

FLOW DIAGRAM III



Compounds of formula I wherein W is CO and Z is O, may be prepared by reacting a compound of formula IV with the appropriate isocyanate or carbonyl or carbamoyl halide in the presence of a base. Using these and other conventional methods, compounds of formula I may be prepared from readily available starting materials.

Advantageously, the inventive compound of formula I may be utilized in the treatment of central nervous system disorders relating to or affected by the 5-HT6 receptor such as motor, mood, psychiatric, cognitive, neurodegenerative, or the like disorders. Accordingly, the present invention provides a method for the treatment of a disorder of the central nervous system (CNS) related to or affected by the 5-HT6 receptor in a patient in need thereof which comprises providing said patient a therapeutically effective amount of a compound of formula I as described hereinabove. The compounds may be provided by oral or parenteral administration or in any common manner known to be an effective administration of a therapeutic agent to a patient in need thereof.

The therapeutically effective amount provided in the treatment of a specific CNS disorder may vary according to the specific condition(s) being treated, the size, age and response pattern of the patient, the severity of the disorder, the judgment of the attending physician and the like. In general, effective amounts for daily oral administration may be about 0.01 to 1,000 mg/kg, preferably about 0.5 to 500 mg/kg and effective amounts for parenteral administration may be about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg.

In actual practice, the compounds of the invention are provided by administering the compound or a precursor thereof in a solid or liquid form, either neat or in combination with one or more conventional pharmaceutical carriers or excipients. Accordingly, the present invention provides a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I as described hereinabove.

Solid carriers suitable for use in the composition of the invention include one or more substances which may

also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aides, binders, tablet-disintegrating agents or encapsulating materials. In powders, the carrier may be a finely divided solid which is in admixture with a finely divided compound of formula I. In tablets, the formula I compound may be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. Said powders and tablets may contain up to 99% by weight of the formula I compound. Solid carriers suitable for use in the composition of the invention include calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Any pharmaceutically acceptable liquid carrier suitable for preparing solutions, suspensions, emulsions, syrups and elixirs may be employed in the composition of the invention. Compounds of formula I may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a pharmaceutically acceptable oil or fat, or a mixture thereof. Said liquid composition may contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, coloring agents, viscosity regulators, stabilizers, osmo-regulators, or the like. Examples of liquid carriers suitable for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) or their derivatives, or oils (e.g., fractionated coconut oil and

arachis oil). For parenteral administration the carrier may also be an oily ester such as ethyl oleate or isopropyl myristate.

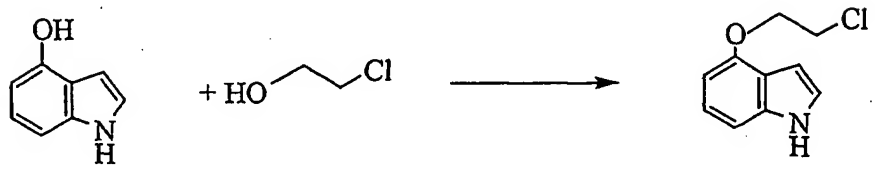
Compositions of the invention which are sterile solutions or suspensions are suitable for intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions may also be administered intravenously. Inventive compositions suitable for oral administration may be in either liquid or solid composition form.

For a more clear understanding, and in order to illustrate the invention more clearly, specific examples thereof are set forth hereinbelow. The following examples are merely illustrative and are not to be understood as limiting the scope and underlying principles of the invention in any way.

Unless otherwise stated, all parts are parts by weight. The terms HPLC and NMR designate high performance liquid chromatography and nuclear magnetic resonance, respectively. The terms EtOAc and Et_2O designate ethyl acetate and diethyl ether, respectively.

EXAMPLE 1

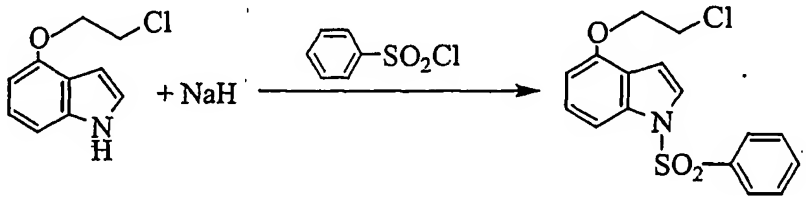
Preparation of 4-(2-Chloroethoxy)-1H-Indole



A solution of 4-hydroxyindole (3.99 g, 30 mmol), 2-chloroethanol (6.03 ml, 90 mmol) and triphenylphosphine (23.6 g, 90 mmol) in tetrahydrofuran is treated with diethyl azodicarboxylate (14.1 ml, 90 mmol) under nitrogen at room temperature, stirred for 2 hr at room temperature and concentrated *in vacuo* to give a residue. Cooled diethyl ether is added to the residue and the solid triphenylphosphine oxide is precipitated and removed by filtration. The filtrate is concentrated and purified by flash chromatography (silica gel, EtOAc/hexane: 1.5/8.5) to give an oil. After trituration with Et_2O/hexane (1/10), the title compound is obtained as a white solid, 4.8 g (82%) mp 60°C, identified by NMR and mass spectral analyses.

EXAMPLE 2

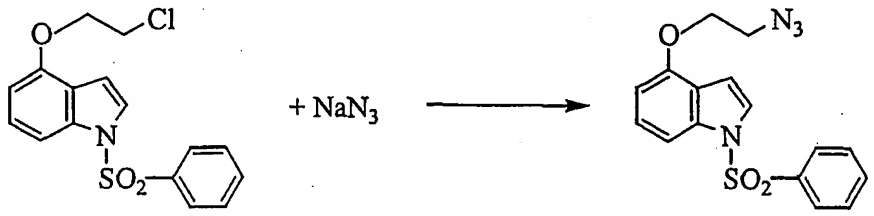
Preparation of 4-(2-Chloroethoxy)-1-(phenylsulfonyl)-1H-Indole



A stirred solution of 4-(2-chloroethoxy)-1H-indole (3.4 g, 17.4 mmol) in tetrahydrofuran is treated with sodium hydride (60% in mineral oil, 1.04 g, 26.1 mmol) under nitrogen at room temperature, stirred for 30 minutes, treated with benzenesulfonyl chloride (3.4 mL, 26.1 mmol) stirred at room temperature overnight and treated with saturated $NaHCO_3$ and EtOAc. The resultant phases are separated. The aqueous phase is extracted with EtOAc and the combined organic phase is washed sequentially with H_2O and saturated NaCl, dried over $MgSO_4$ and concentrated *in vacuo* to give a residue. The residue is purified by flash chromatography (silica gel, EtOAc/hexane: 2/8) to give the title compound as an off-white solid, 4.94 g (86%), mp 85-87°C, identified by NMR and mass spectral analyses.

EXAMPLE 3

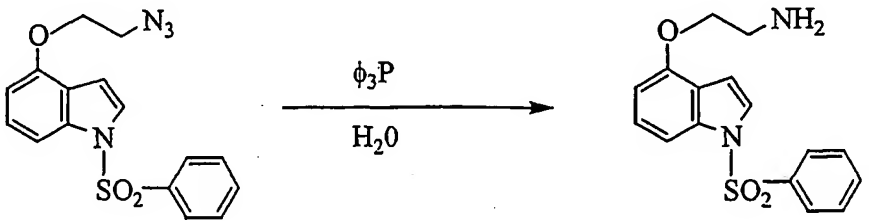
Preparation of 2-{[1-(Phenylsulfonyl)-1H-indole-4-yl]oxy}ethylazide



A suspension of 4-(2-chloroethoxy)-1-(phenylsulfonyl)-1H-indole (3.35 g, 10 mmol) and sodium azide (1.95 g, 30 mmol) in anhydrous dimethylformamide is stirred under nitrogen for 20 hr at 60 °C, poured into water and extracted with diethyl ether. The extracts are combined, washed sequentially with 1N HCl, H_2O and saturated NaCl, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title product as an off-white solid, 3.3 g (96%), identified by NMR and mass spectral analyses.

EXAMPLE 4

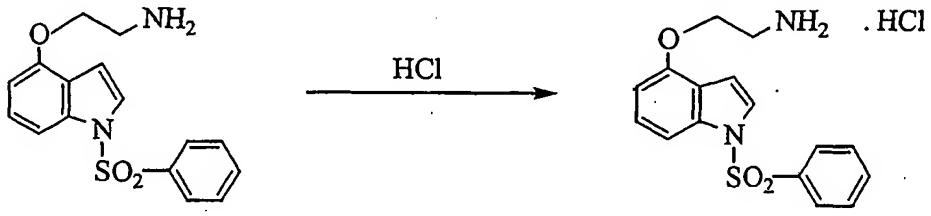
Preparation of 2-{[1-(Phenylsulfonyl)-1H-indole-4-yl]oxy}ethylamine



A mixture of 2-{[1-(phenylsulfonyl)-1H-indole-4-yl]oxy}ethylazide (3.3 g, 9.6 mmol) and triphenylphosphine (3.67 g, 14 mmol) in tetrahydrofuran and water is stirred under nitrogen for 24 hr at room temperature and filtered. The filtrate is concentrated *in vacuo* and the resultant residue is purified by flash chromatography (silica gel, EtOAc/MeOH/NH_4OH: 8.5/1.5/0.05) to afford the title compound as an off-white solid, 2.54 g (80%), mp 71-73°C, identified by NMR and mass spectral analyses.

EXAMPLE 5

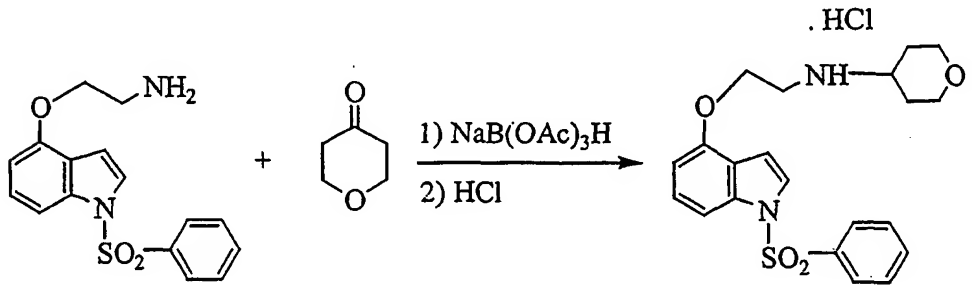
Preparation of 2-{[1-(Phenylsulfonyl)-1H-indole-4-yl]oxy}ethylamine hydrochloride



A solution of 2-{[1-(phenylsulfonyl)-1H-indole-4-yl]oxy}ethylamine (0.20 g, 0.63 mmol) in ethyl acetate is treated with HCl in diethyl ether (1M, 0.7 ml) and filtered. The filtercake is dried *in vacuo* to afford the title product as a pink solid, 0.21 g, mp 198-200°C, identified by NMR and mass spectral analyses.

EXAMPLE 6

Preparation of N-(2-{[1-(Phenylsulfonyl)-1H-indol-4-yl]oxy}ethyl)tetrahydro-2H-pyran-4-amine hydrochloride

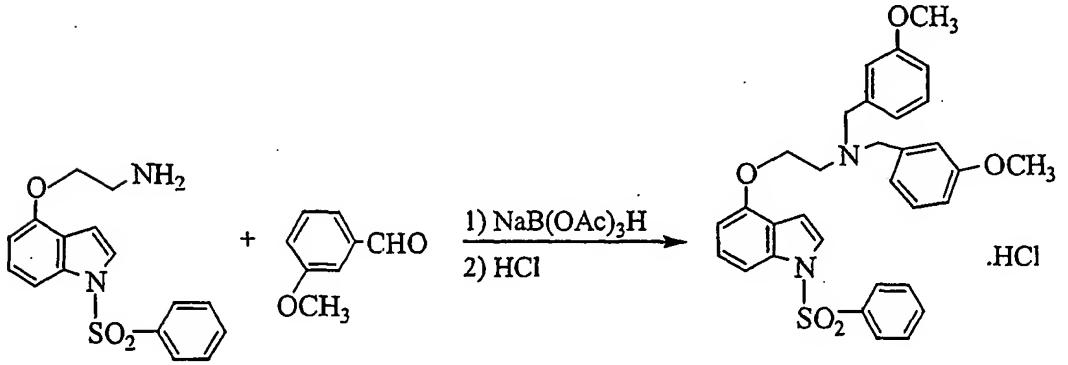


A mixture of 2-{[1-(phenylsulfonyl)-1H-indole-4-yl]oxy}ethylamine (0.316 g, 1.0 mmol), tetrahydro-4H-pyran-4-one (0.09 ml, 1.00 mmol) and sodium triacetoxyborohydride (0.312 g, 1.4 mmol) in 1,2-dichloroethane is treated with acetic acid (0.06 ml) at room temperature, stirred under nitrogen for 18 hr, quenched with concentrated aqueous NH_4OH and diluted with methylene chloride and water. The aqueous layer is separated and extracted with methylene chloride. The organic layer and extracts are combined, washed with saturated NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/MeOH/NH_4OH: 9/1/0.05) to afford the free amine of the title product as a clear oil, 0.36 g (90%).

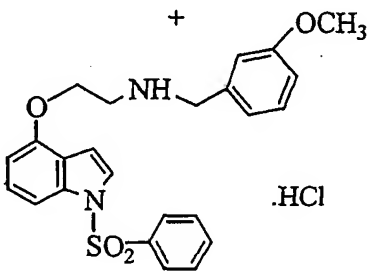
The HCl salt is prepared in HCl and ethyl acetate to give the title product as an off-white solid, mp 229-230°C, identified by NMR and mass spectral analyses.

EXAMPLES 7a AND 7b

Preparation of (a) N,N-Bis(3-methoxybenzyl)-N-(2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethylamine and (b) N-(3-methoxybenzyl)-N-(2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethylamine hydrochloride



(a)



(b)

A mixture of 2-{[1-(phenylsulfonyl)-1H-indole-4-yl]oxy}ethylamine (0.316 g, 1.0 mmol), *m*-anisaldehyde (0.12 ml, 1.0 mmol) and sodium triacetoxyborohydride (0.312 g, 1.4 mmol) in 1,2-dichloroethane is treated with acetic acid (0.06 ml) at room temperature, stirred under nitrogen at room temperature for 18 hr, quenched with

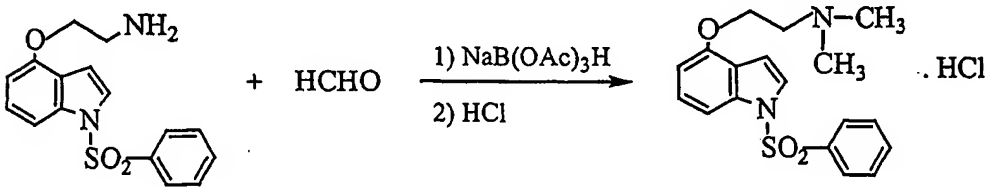
concentrated aqueous NH_4OH and diluted with methylene chloride and water. The aqueous layer is separated and extracted with methylene chloride. The organic layer and extracts are combined and washed with saturated NaCl dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The residue is purified by flash chromatography (silica gel, EtOAc/MeOH/NH_4OH: 9.5/0.5/0.05) to afford the free amine of 7a, 0.20 g (36%) as a clear oil and the free amine of 7b, 0.135 g (31%) as a clear oil.

The HCl salt of 7a is prepared in ethyl acetate and anhydrous HCl in ether to give the 7a title product as a white solid, mp 194-196°C, identified by NMR and mass spectral analyses.

The HCl salt of 7b is prepared in ethyl acetate and anhydrous HCl in ether to give the 7b title product as a white solid, mp 189-190°C, identified by NMR and mass spectral analyses.

Example 8

Preparation of N,N-Dimethyl-N-(2-{[1-phenylsulfonyl)-1H-indol-4-yl]oxy}ethylamine hydrochloride



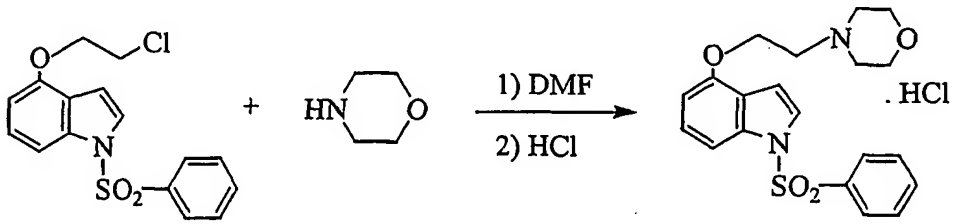
A mixture of 2-{[1-(phenylsulfonyl)-1H-indole-4-yl]oxy}ethylamine (0.316 g, 1.0 mmol), formaldehyde (0.16

ml, 2.0 mmol) and sodium triacetoxyborohydride (0.446 g, 2.0 mmol) in 1,2-dichloroethane is stirred under nitrogen at room temperature for 48 hr, quenched with concentrated aqueous NH_4OH and diluted with methylene chloride. The aqueous layer is separated and extracted with methylene chloride. The organic layer and extracts are combined, washed with saturated NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/MeOH/NH_4OH: 9.5/0.5/0.03) to afford the free amine as a white solid, 0.215 g (36%).

The HCl salt is prepared in ethyl acetate and anhydrous HCl in ether to give the title product as a white solid, mp 140-142°C, identified by NMR and mass spectral analyses.

EXAMPLE 9

Preparation of 4-(2-Morpholin-4-ylethoxy)-1-(phenyl-sulfonyl)-1H-indole hydrochloride



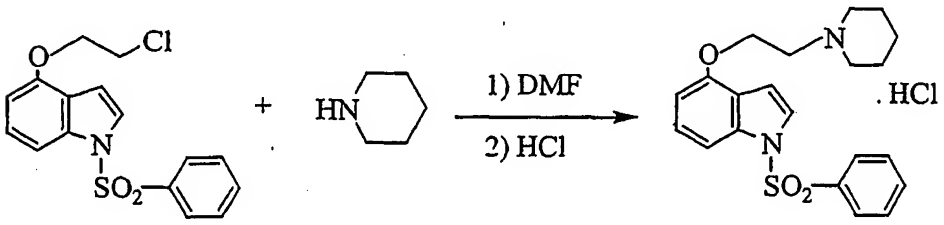
A mixture of 4-(2-chloroethoxy)-1-phenylsulfonyl-1H-indole (0.50 g, 1.5 mmol) and morpholine (1.30 ml, 15 mmol) in dimethylformamide (DMF) is stirred under nitrogen at 80°C for 18 hr, cooled to room temperature,

quenched with water and extracted with diethyl ether. The combined ether extracts are washed with saturated sodium chloride, dried over $MgSO_4$, and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/MeOH/NH_4OH: 9.7/0.5/0.05) to afford the free amine as a white solid, 0.48 g (83%).

The HCl salt is prepared in ethyl acetate and HCl to afford the title product as a white solid, mp 140-142°C, identified by NMR and mass spectral analyses.

EXAMPLE 10

Preparation of 1-(Phenylsulfonyl)-4-(2-piperidin-1-ylethoxy)-1H-indole hydrochloride



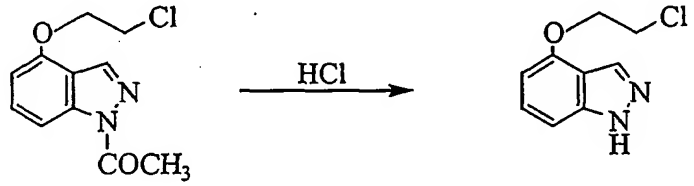
A mixture of 4-(2-chloroethoxy)-1-phenylsulfonyl-1H-indole (0.323 g, 1.0 mmol) and piperidine (0.99 ml, 10 mmol) in dimethylformamide (DMF) is stirred under nitrogen at 80°C for 18 hr, cooled to room temperature, quenched with water and extracted with diethyl ether. The ether extracts are combined, washed with saturated sodium chloride, dried over $MgSO_4$ and concentrated *in*

vacuo. The resultant residue is purified by flash chromatography (silica gel, EtOAc/MeOH/NH_4OH: 9.7/0.5/0.05) to afford the free amine as a light yellow oil 0.34 g (88%).

The HCl salt is prepared in ethyl acetate and HCl to give the title product as a light yellow solid, mp 131-133°C, identified by NMR and mass spectral analyses.

EXAMPLE 11

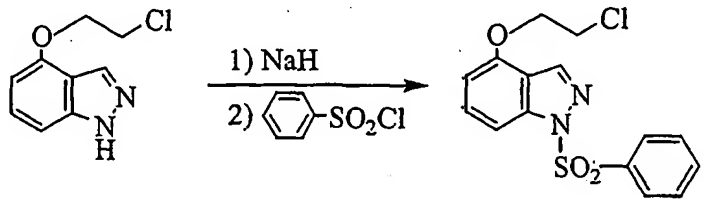
Preparation of 4-(2-Chloroethoxy)-1H-indazole



A stirred solution of 1-acetyl-4-(2-chloroethoxy)-indazole (1.50 g, 6.3 mmol) in methanol is treated with hydrochloric acid (6.3 ml, 1.0 M HCl in Et_2O, 6.3 mmol) at room temperature, heated at 65°C under nitrogen for 18 hr, cooled to room temperature and concentrated *in vacuo*. The resultant residue is neutralized with 1N NaOH (6.0 ml) and diluted with H_2O and ethyl acetate. The phases are separated and the aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with water and saturated NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to afford the title product (1.2 g) as a yellow solid, identified by NMR and mass spectral analyses.

EXAMPLE 12

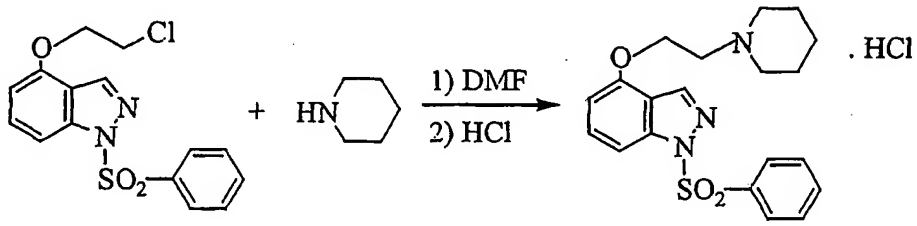
Preparation of 4-(2-Chloroethoxy)-1-(phenylsulfonyl)-1H-indazole



A stirred solution of 4-(2-chloroethoxy)-1H-indazole (1.1 g, 5.59 mmol) in tetrahydrofuran is treated with NaH (0.335 g, 60% in mineral oil, 8.39 mmol) under nitrogen at room temperature, stirred for 30 minutes, treated with benzenesulfonyl chloride (0.86 ml, 6.71 mmol), stirred at room temperature for 18 hr, quenched with water and diluted with ethyl acetate. The phases are separated and the organic phase is washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/hexane: 3/7) to give the desired product as a white solid, 1.75 g (93%), mp 102-104°C, identified by NMR and mass spectral analyses.

EXAMPLE 13

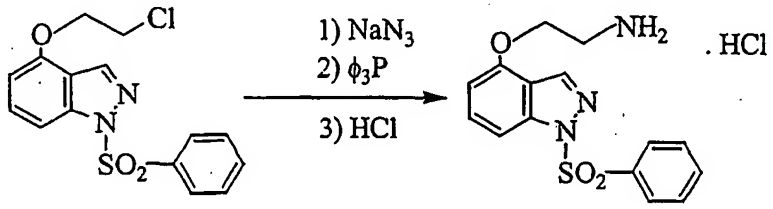
Preparation of 1-Phenylsulfonyl)-4-[1-piperidinyl)ethoxy]-1H-indazole hydrochloride



A mixture of 4-(2-chloroethoxy)-1-(phenylsulfonyl)-1H-indazole (0.337 g, 1.0 mmol) and piperidine (0.20 ml, 2.0 mmol) in N,N-dimethylformamide (DMF)is stirred under nitrogen at 80°C for 18 hr, cooled, quenched with ice-water and diluted with ethyl acetate. The phases are separated. The aqueous phase is extracted with ethyl acetate. The organic phases are combined, washed with water and saturated NaCl, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil residue. The residue is dissolved in ethyl acetate, treated with 1M HCl (1 ml, 1M HCl in Et_2O) and filtered. The filtercake is dried under vacuum to afford the title product as an off-white solid, 354 mg, mp 87-89°C, identified by NMR and mass spectral analyses.

EXAMPLE 14

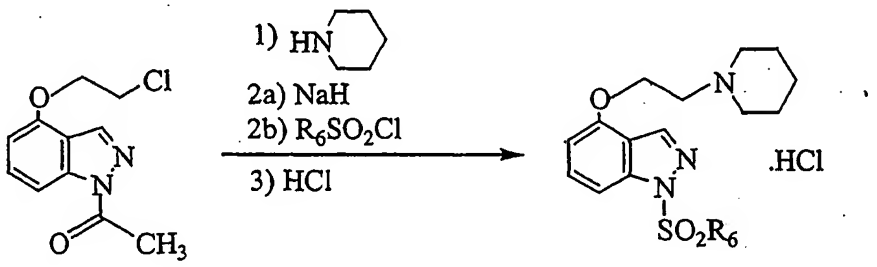
Preparation of 2-{[1-Phenylsulfonyl)-1H-indazol-4-yl]oxy}ethylamine hydrochloride



A suspension of 4-(2-chloroethoxy)-1-(phenylsulfonyl)-1H-indazole (0.66 g, 1.96 mmol) and sodium azide (0.382 g, 5.87 mmol) in N,N-dimethylformamide is stirred under nitrogen at 60°C for 24 hr, cooled, quenched with 1N HCl and extracted with ethyl acetate. The combined extracts are washed with water and saturated NaCl, dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow solid residue. The residue is dissolved in tetrahydrofuran, treated with triphenylphosphine (0.771 g, 2.94 mmol) and water, stirred at room temperature for 18 hr and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/2M NH3 in MeOH: 90/10) to give the free amine (0.41 g) as a gum. The gum is dissolved in ethyl acetate and treated with anhydrous HCl in ether. The reaction mixture is filtered and the filtercake is air-dried to give the title product as a white solid, mp 201-203°C, identified by NMR and mass spectral analyses.

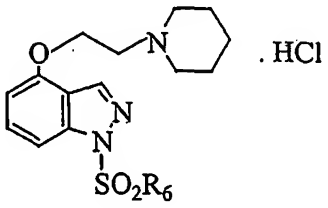
EXAMPLES 15 and 16

Preparation of 1-(Arylsulfonyl)-4-[2-(1-piperidinyl)-ethoxy]-1H-indazole hydrochloride



Using essentially the same procedures described in Examples 11, 12 and 13 and employing the appropriate arylsulfonyl chloride, the compounds shown in Table I are obtained and identified by NMR and mass spectral analyses.

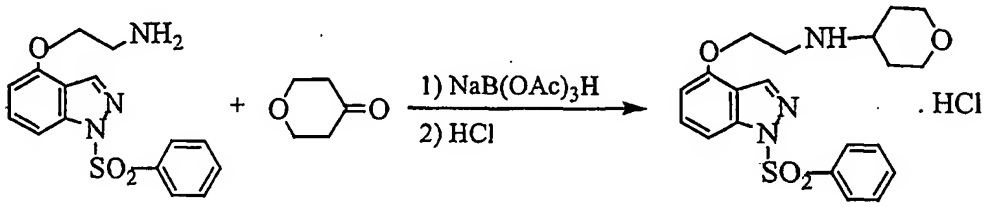
Table I



Ex. No.	R_6	mp °C	M+H
15	4-nitrophenyl	117-119	431
16	4-fluorophenyl	122 (dec)	404

EXAMPLE 17

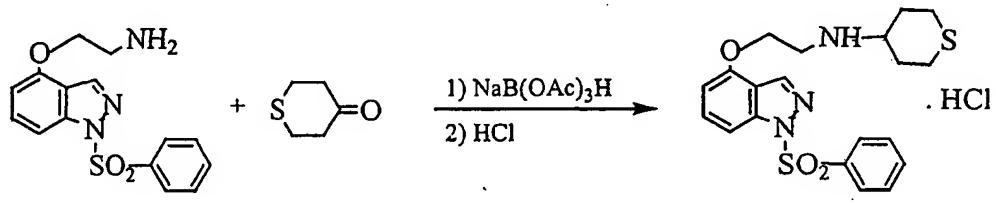
Preparation of N-(2-{[1-Phenylsulfonyl)-1H-indazol-4-yl]oxy}ethyl)tetrahydro-2H-pyran-4-amine



A suspension of 2-{[1-(phenylsulfonyl)-1H-indazol-4-yl]oxy}ethylamine (0.10 g, 0.31 mmol), tetrahydro-4H-pyran-4-one (0.03 ml, 0.31 mmol) and sodium triacetoxyborohydride (0.097 g, 0.43 mmol) in 1,2-dichloroethane is treated with acetic acid (0.03 ml) at room temperature, allowed to stir under nitrogen at room temperature for 18 hr, quenched with 1N NaOH (2 ml) and diluted with water and a 4:1 mixture of methylene chloride:isopropanol. The phases are separated and the aqueous phase is further extracted with a 4:1 mixture of methylene chloride:isopropanol. The organic phases are combined, washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resultant residue is dissolved in a 4:1 mixture of ethyl acetate:isopropanol, treated with anhydrous HCl in ether and filtered to obtain the title product as a white solid, mp 173-175°C, identified by NMR and mass spectral analyses.

EXAMPLE 18

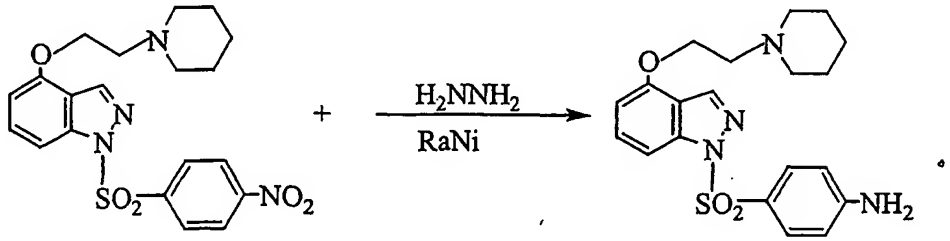
Preparation of N-(2-{[1-Phenylsulfonyl)-1H-indazol-4-yl]oxy}ethyl)tetrahydro-2H-thiopyran-4-amine hydrochloride



Using essentially the same procedures described in Example 17 and substituting tetrahydrothiopyran-4-one as the reactant, the title product is obtained as a white solid, mp 182-184°C, identified by NMR and mass spectral analyses.

EXAMPLE 19

Preparation of 4-({4-[2-(1-Piperidinyl)ethoxy]-1H-indazol-1-yl}sulfonyl)aniline



A stirred solution of 1-[(4-nitrophenyl)sulfonyl]-4-[2-(1-piperidinyl)ethoxy]1H-indazole (0.39 g, 0.91 mol) in methanol is treated with Raney Nickel followed by

hydrazine (0.2 ml, 6.3 mmol), stirred at 0°C for 2 hr and decanted. The catalyst is washed with a methanol: methylene chloride 3:7 mixture. The washes and supernatant are combined and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silicagel, EtOAc/2M NH_3 in methanol 8:2) to give the title product as a white solid, 0.15 g, mp 149-150 °C (dec), identified by NMR and mass spectral analyses.

EXAMPLE 20

Comparative Evaluation of 5-HT6 Binding Affinity of Test Compounds

The affinity of test compounds for the serotonin 5-HT6 receptor is evaluated in the following manner. Cultured Hela cells expressing human cloned 5-HT6 receptors are harvested and centrifuged at low speed (1,000 x g) for 10.0 min to remove the culture media. The harvested cells are suspended in half volume of fresh physiological phosphate buffered saline solution and recentrifuged at the same speed. This operation is repeated. The collected cells are then homogenized in ten volumes of 50 mM Tris.HCl (pH 7.4) and 0.5 mM EDTA. The homogenate is centrifuged at 40,000 x g for 30.0 min and the precipitate is collected. The obtained pellet is resuspended in 10 volumes of Tris.HCl buffer and recentrifuged at the same speed. The final pellet is suspended in a small volume of Tris.HCl buffer and the tissue protein content is determined in aliquots of 10-25

µl volumes. Bovine Serum Albumin is used as the standard in the protein determination according to the method described in Lowry et al., J. Biol. Chem., 193:265 (1951). The volume of the suspended cell membranes is adjusted to give a tissue protein concentration of 1.0 mg/ml of suspension. The prepared membrane suspension (10 times concentrated) is aliquoted in 1.0 ml volumes and stored at -70° C until used in subsequent binding experiments.

Binding experiments are performed in a 96 well microtiter plate format, in a total volume of 200 µl. To each well is added the following mixture: 80.0 µl of incubation buffer made in 50 mM Tris.HCl buffer (pH 7.4) containing 10.0 mM $MgCl_2$ and 0.5 mM EDTA and 20 µl of [^{3}H]-LSD (S.A., 86.0 Ci/mmol, available from Amersham Life Science), 3.0 nM. The dissociation constant, K_D of the [^{3}H]LSD at the human serotonin 5-HT6 receptor is 2.9 nM, as determined by saturation binding with increasing concentrations of [^{3}H]LSD. The reaction is initiated by the final addition of 100.0 µl of tissue suspension. Nonspecific binding is measured in the presence of 10.0 µM methiothepin. The test compounds are added in 20.0 µl volume.

The reaction is allowed to proceed in the dark for 120 min at room temperature, at which time, the bound ligand-receptor complex is filtered off on a 96 well unifilter with a Packard Filtermate® 196 Harvester. The bound complex caught on the filter disk is allowed to air dry and the radioactivity is measured in a Packard TopCount® equipped with six photomultiplier detectors, after the addition of 40.0µl Microscint®-20 scintillant

to each shallow well. The unifilter plate is heat-sealed and counted in a PackardTopCount® with a tritium efficiency of 31.0%.

Specific binding to the 5-HT6 receptor is defined as the total radioactivity bound less the amount bound in the presence of 10.0μM unlabeled methiothepin. Binding in the presence of varying concentrations of test compound is expressed as a percentage of specific binding in the absence of test compound. The results are plotted as log % bound versus log concentration of test compound. Nonlinear regression analysis of data points with a computer assisted program Prism® yielded both the IC_{50} and the K_i values of test compounds with 95% confidence limits. A linear regression line of data points is plotted, from which the IC_{50} value is determined and the K_i value is determined based upon the following equation:

$$K_i = IC_{50} / (1 + L/K_D)$$

where L is the concentration of the radioactive ligand used and K_D is the dissociation constant of the ligand for the receptor, both expressed in nM.

Using this assay, the following Ki values are determined and compared to those values obtained by representative compounds known to demonstrate binding to the 5-HT6 receptor. The data are shown in Table II, below.

Table II

Test Compound (Ex. No.)	5-HT6 Binding Ki (nM)
5	2.0
6	6.0
7a	94% @ 1μM*
7b	95% @ 1μM*
8	4.0
9	92% @ 1μM*
10	7.0
13	2.0
14	1.0
15	76% @ 1μM*
16	19.0
17	6.0
18	11.0
19	1.0

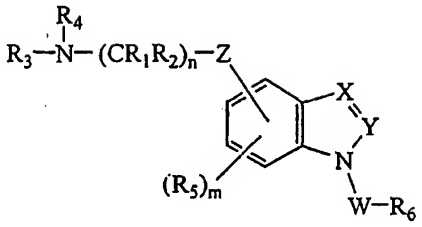
Comparative Examples	5-HT6 Binding Ki (nM)
Clozapine	6.0
Loxapine	41.4
Bromocriptine	23.0
Methiothepin	8.3
Mianserin	44.2
Olanzepine	19.5

*% inhibition at 1μM concentration

As can be seen from the results set forth above, the compounds of the present invention have a high degree of affinity for the serotonin 5-HT6 receptor.

WHAT IS CLAIMED IS:

1. A compound of formula I



(I)

wherein

W is SO_2, CO, CONH, CSNH or CH_2;

X is CR_7 or N;

Y is CR_8 or N with the proviso that when X is N, then Y must be CR_8;

Z is O, SO_p or NR_9;

R_1 and R_2 are each independently H or C_1-C_6alkyl;

n is an integer of 2, 3 or 4;

R_3 and R_4 are each independently H, $CNR_{10}NR_{11}R_{12}$, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted, or R_3 and R_4 may be taken together with the atom to which they are attached to form an optionally substituted 3- to 6-membered ring optionally containing an additional heteroatom selected from O, N or S;

R_5 is H, halogen, CN, OR_{13}, CO_2R_{14}, $CONR_{15}R_{16}$, $CNR_{17}NR_{18}R_{19}$, $SO_2NR_{20}R_{21}$, SO_qR_{22} or a C_1-C_6alkyl, C_2-C_6alkenyl,

C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

m is an integer of 1, 2 or 3;

p and q are each independently 0 or an integer of 1 or 2;

R_6 is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

R_7 and R_8 are each independently H, halogen or a C_1-C_6 alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_9 is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{10}, R_{11}, R_{12}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19} are each independently H or C_1-C_4alkyl;

R_{13} is H, COR_{23} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{14} is H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted;

R_{20} and R_{21} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{22} and R_{23} are each independently an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein W is SO_2.

3. A compound according to claim 1 or claim 2 wherein Z is O.

4. A compound according to any one of claims 1 to 3 wherein n is 2.

5. A compound according to any one of claims 1 to 4 wherein R_6 is an aryl or heteroaryl group each optionally substituted.

6. A compound according to any one of claims 1 to 5 wherein X is CR_7 and R_5 and R_7 are H.

7. A compound according to any one of claims 1 to 6 wherein R_1 and R_2 are H.

8. A compound according to any one of claims 1 to 7 wherein R_3 and R_4 are taken together with the atom to which they are attached to form a 5- or 6-membered ring optionally containing one oxygen atom.

9. A compound according to claim 1 selected from the group consisting of:

2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethylamine;

4-(2-morpholin-4-ylethoxy)-1-(phenylsulfonyl)-1H-indole;

1-(phenylsulfonyl)-4-(2-piperidin-1-ylethoxy)-1H-indole;

N-(2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethyl)tetrahydro-2H-pyran-4-amine;

N,N-bis(3-methoxybenzyl)-2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethanamine;

N-(3-methoxybenzyl)-2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethanamine;

N,N-dimethyl-2-{[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}ethanamine;

1-(phenylsulfonyl)-4-[2-(1-piperidinyl)ethoxy]-1*H*-indazole;

2-{[1-(phenylsulfonyl)-1*H*-indazol-4-yl]oxy}ethylamine;

N-(2-{[1-(phenylsulfonyl)-1*H*-indazol-4-yl]oxy}ethyl)tetrahydro-2*H*-pyran-4-amine;

N-(2-{[1-(phenylsulfonyl)-1*H*-indazol-4-yl]oxy}ethyl)tetrahydro-2*H*-thiopyran-4-amine;

1-[(4-nitrophenyl)sulfonyl]-4-[2-(1-piperidinyl)ethoxy]-1*H*-indazole;

1-[(4-fluorophenyl)sulfonyl]-4-[2-(1-piperidinyl)ethoxy]-1*H*-indazole;

4-({4-[2-(1-piperidinyl)ethoxy]-1*H*-indazol-1-yl}sulfonyl)aniline; and

a pharmaceutically acceptable salt thereof.

10. A method for the treatment of a disorder of the central nervous system related to or affected by the 5-HT6 receptor in a patient in need thereof which comprises providing to said patient a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1 to 9.

11. A method according to claim 10 wherein said disorder is a motor disorder, anxiety disorder or cognitive disorder.

12. A method according to claim 10 wherein said disorder is schizophrenia or depression.

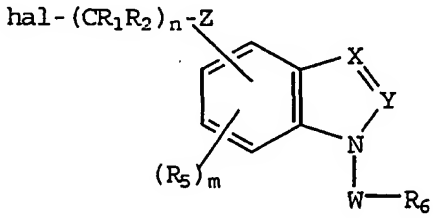
13. A method according to claim 11 wherein said cognitive disorder is attention deficit disorder.

14. A method according to claim 11 wherein said cognitive disorder is Alzheimer's disease or Parkinson's disease.

15. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of formula I as claimed in any one of claims 1 to 9.

16. A method for the preparation of a compound as claimed in claim 1 which comprises one of the following:

a) reacting a compound of formula (Va)



(Va)

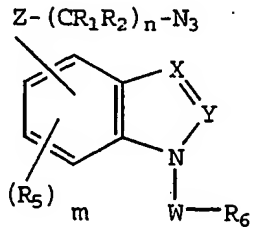
wherein hal is a halogen, e.g. chlorine or bromine and n, m, W, X, Y, Z, R_1, R_2, R_5 and R_6 are as defined in Claim 1, with an amine of formula

HNR_3R_4

wherein R_3 and R_4 are as defined in claim 1, said reactants protected on reactive sites and/or on reactive substituent groups as required, and removing any protecting groups to give a corresponding compound of formula (I);

or

b) reducing a compound of formula (VIa)

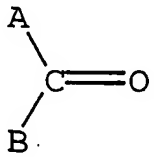


(V1a)

wherein n, m, Z, W, X, Y, R_1, R_2, R_3, R_5 and R_6 are as defined in claim 1 to give a compound of formula (I) wherein R_3 and R_4 are both H;

or

d) reductively alkylating a compound of formula (I) as defined in Claim 1 wherein R_3 and R_4 are hydrogen with an alkylating agent of formula



where A and B independently represent H, or optionally substituted alkyl of 1-5 carbon atoms, alkenyl of 2-5 carbon atoms, alkynyl of 2-5 carbon atoms, aryl, heteroaryl or cycloheteroalkyl,
or A and B together represent an optionally substituted 3-6 membered cycloalkyl or cycloheteroalkyl ring,
to give a compound of formula (I)wherein R_3 and R_4 are both methyl, or R_3 is hydrogen and R_4 is optionally substituted alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, aryl-CH_2-, heteroaryl-CH_2-, cycloalkyl or cycloheteroalkyl;

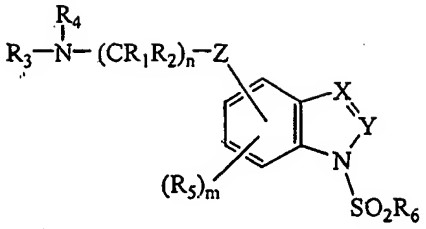
or

d) converting a compound of formula (I) having a reactive substituent group to a different compound of formula I;

or

e) converting a basic compound of formula (I) to an acid addition salt or vice versa.

17. A method for the preparation of a compound of formula Ia



(Ia)

wherein

X is CR_7 or N;

Y is CR_8 or N with the proviso that when X is N, then Y must be CR_8;

Z is O, SO_p or NR_9;

R_1 and R_2 are each independently H or C_1-C_6alkyl;

n is an integer of 2, 3 or 4;

R_3 and R_4 are each independently H, $CNR_{10}NR_{11}R_{12}$, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted, or R_3 and R_4 may be taken together with the atom to which they are attached to form an optionally substituted 3- to 6-membered ring optionally containing an additional heteroatom selected from O, N or S;

R_5 is H, halogen, CN, OR_{13}, CO_2R_{14}, $CONR_{15}R_{16}$, $CNR_{17}NR_{18}R_{19}$, $SO_2NR_{20}R_{21}$, SO_qR_{22} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

m is an integer of 1, 2 or 3;

p and q are each independently 0 or an integer of 1 or 2;

R_6 is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

R_7 and R_8 are each independently H, halogen or a C_1-C_6 alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_9 is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{10}, R_{11}, R_{12}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19} are each independently H or C_1-C_4alkyl;

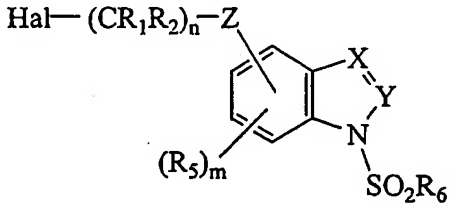
R_{13} is H, COR_{23} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{14} is H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted;

R_{20} and R_{21} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{22} and R_{23} are each independently an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group

which method comprises reacting a compound of formula V'



(V')

wherein Hal is Cl, Br or I and X, Y, Z, n, m, R_1, R_2, R_5 and R_6 are as defined hereinabove with an amine, HNR_3R_4,

wherein R_3 and R_4 are defined hereinabove optionally in the presence of a solvent to give the desired compound of formula Ia.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/01950

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/08 C07D405/12 C07D231/56 C07D409/12 A61P25/28
A61K31/4045 A61K31/416 A61K31/4184

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 06079 A (SMITHKLINE BEECHAM PLC ;GASTER LARAMIE MARY (GB)) 29 February 1996 (1996-02-29) page 6, line 3-18; claim 1; examples 4-7,9 ---	1-17
X	WO 95 17398 A (SMITHKLINE BEECHAM PLC ;GASTER LARAMIE MARY (GB); WYMAN PAUL ADRIA) 29 June 1995 (1995-06-29) page 5, line 3-16; claim 1; example 4 ---	1-17
X	WO 97 31635 A (LILLY CO ELI ;GITTER BRUCE D (US); IYENGAR SMRITI (US)) 4 September 1997 (1997-09-04) claim 1; examples 70-83,85-96,99-103,105-113,115-131,133-136 ,138-143 examples 146-150 page 93, line 13-21 --- -/--	1-9,15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2002	05/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gavriliu, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/01950

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 35488 A (DU PONT PHARM CO) 22 June 2000 (2000-06-22) page 277, line 5 -page 278, line 20; claim 1; example 47	1-9,15
X	WO 00 46198 A (FAULL ALAN WELLINGTON ;KETTLE JASON (GB); ASTRAZENECA US LIMITED () 10 August 2000 (2000-08-10) page 3, line 13-18; claims 1,3	1-9,15
X	WO 97 25041 A (LILLY CO ELI) 17 July 1997 (1997-07-17) page 342, line 34 -page 344, line 4; claim 1; examples 326-335	1-17
A	GB 2 341 549 A (MERCK SHARP & DOHME) 22 March 2000 (2000-03-22) page 2, line 17-22; claim 1 page 7, line 19-24	1-17
E	WO 02 14273 A (LOVELL PETER JOHN ;BROMIDGE STEVEN MARK (GB); MOSS STEPHEN FREDERI) 21 February 2002 (2002-02-21) page 9, line 1-30 page 33, line 28-34	1-15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty as regards the compounds defined by the claim 1 , when W is CH2 (see e.g. WO 97/31635; WO 00/35488 and WO 97/25041). So it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim is impossible. Consequently, the search has been restricted to claim 1 , wherein W is SO2, CO, CONH or CSNH.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/01950

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/01950

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9606079	A	29-02-1996	AT	199543 T	15-03-2001
			DE	69520279 D1	12-04-2001
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			EP	1150954 A1	07-11-2001
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			NO	20013808 A	02-10-2001
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			CA	2242579 A1	17-07-1997
			EP	0871442 A1	21-10-1998
			JP	2000501107 T	02-02-2000
			WO	9725041 A1	17-07-1997
			US	2002007071 A1	17-01-2002
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WO 0214273	A	21-02-2002	WO	0214273 A1	21-02-2002